Objective: To determine the frequency of complications and adverse outcomes due to herpes zoster ophthalmicus before and after the introduction of oral antiviral medications in a community-based setting.

Methods: We identified all Olmsted County, Minnesota, residents diagnosed with acute herpes zoster ophthalmicus from 1976 through 1998. The frequencies of complications within 6 months of disease onset were compared between untreated patients vs those treated with antivirals.

Main Outcome Measures: Defined complications were ocular sequelae due to herpes zoster ophthalmicus. Adverse outcomes included visual acuity of 20/200 or worse, trichiasis, or eyelid malposition requiring surgical treatment.

Results: A total of 202 patients had been treated with antivirals, and 121 had not. Neurotrophic keratitis was the only complication that was less likely in the treated group (3.3% vs 0%; \( P = .02 \)). The probability of an adverse outcome at 5 and 10 years was 8.9% among untreated patients and 2.1% among treated patients \((P = .009)\). Among patients who had been treated, the mean time from symptom onset to initiation of therapy was 4.8 days in those who developed stromal keratitis, corneal edema, scleritis, uveitis, or glaucoma compared with 3.8 days in those who did not \((P = .006)\).

Conclusions: Neurotrophic keratitis was less frequent among patients who received antiviral therapy. However, among treated patients, development of a serious inflammatory complication was associated with a delay in therapy. Most important, adverse outcomes were less probable in the treated group. These data may support the early and routine use of systemic antiviral therapy for acute herpes zoster ophthalmicus.

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Ernest A. Severson, MD; Keith H. Baratz, MD; David O. Hodge, MS; James P. Burke, PhD

Herpes Zoster Ophthalmicus in Olmsted County, Minnesota Have Systemic Antivirals Made a Difference?

From Mayo Medical School (Dr Severson) and the Departments of Ophthalmology (Dr Baratz) and Epidemiology and Biostatistics (Dr Burke and Mr Hodge), Mayo Clinic, Rochester, Minn. Dr Severson is now with the University of North Dakota, Grand Forks.

The authors have no relevant financial interest in this article.
Table 1. Diagnostic Criteria for Short-term Complications and Adverse Outcomes In Patients With Herpes Zoster Ophthalmicus (HZO)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Diagnostic Criteria</th>
</tr>
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<tbody>
<tr>
<td>Conjunctivitis</td>
<td>Hyperemia or chemosis</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>External inflammation diagnosed by the examining clinician as episcleritis</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Scleral necrosis or severe external inflammation diagnosed by the examining clinician as scleritis</td>
</tr>
<tr>
<td>Epithelial keratitis</td>
<td>Early dendrites: Any elevated nonpunctate epithelial lesion within the first 4 weeks of the onset of HZO</td>
</tr>
<tr>
<td>Late mucus plaques</td>
<td>Any elevated dendritiform or geographic lesion after the first 4 weeks of HZO</td>
</tr>
<tr>
<td>Other</td>
<td>Any epithelial lesion not satisfying criteria for early dendrites or late mucus plaques, usually superficial punctuate keratopathy</td>
</tr>
<tr>
<td>Stromal keratitis</td>
<td>Subepithelial or stromal infiltrate, cells or haze, except for haze caused by edema associated with a diagnosis implicating endothelial dysfunction; any patient in whom a stromal scar or neovascularization was noted was also assumed to have had stromal keratitis, unless another cause was indicated</td>
</tr>
<tr>
<td>Neurotrophic keratitis</td>
<td>Any central epithelial defect or ulcer after the first 4 weeks of HZO in the setting of decreased corneal sensation and not attributed to other specific causes (eg, trauma or infection); chronic superficial punctate keratopathy was not considered to be neurotrophic keratitis unless specifically diagnosed as such by the examining clinician</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>Corneal or stromal thickening or folds, epithelial or stromal edema in the setting of elevated intraocular pressure; not stromal haze or clouding, unless specifically attributed to edema</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Keratoprecipitates or anterior chamber cells, fibrin, or hypopyon</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Any single intraocular pressure elevation greater than 30 mm Hg or any intraocular pressure elevation greater than 22 mm Hg for which the clinician instituted glaucoma therapy; patients with preexisting glaucoma were excluded from analysis of this complication</td>
</tr>
<tr>
<td>Extraocular muscle palsy</td>
<td>Any symptomatic diplopia that began within 4 weeks after the onset of HZO and was confirmed by the examining clinician as being due to extraocular muscle involvement</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Optic nerve dysfunction specifically diagnosed by the examining clinician as being due to HZO</td>
</tr>
<tr>
<td>Retinitis</td>
<td>Retinal infiltrate or scar specifically diagnosed by the examining clinician as being due to HZO</td>
</tr>
<tr>
<td>Severe visual loss</td>
<td>Visual acuity of 20/200 or worse due to specifically described complications of HZO in an eye that formerly had better vision</td>
</tr>
<tr>
<td>Eyelid scar</td>
<td>Any eyelid abnormality, such as malposition, that required surgical intervention for noncosmetic purposes or trichiasis that required treatment</td>
</tr>
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</table>

had stromal keratitis, unless another cause was indicated. Because of the high cost of these medications, the benefit of their routine use has been questioned.29

Established in 1976 to facilitate epidemiologic studies of disease, the Rochester Epidemiology Project (REP) is a medical records linkage system tracking all diagnostic and surgical procedure codes for the residents of Olmsted County, Minnesota.30 The REP includes patients treated at Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals and clinics and has been used in a variety of previous studies to determine trends in incidence rates and outcomes of specific eye diseases.31-35 We used the REP resources as a means of studying the community-based care of HZO before and after the introduction of oral antiviral therapy. Our purpose was to establish whether antiviral therapy during the acute phase of HZO had an impact on the frequency of subsequent ocular complications and on the probability of adverse outcomes caused by the disease.

The resources of the REP were used to identify all Olmsted County residents who sought care for potential acute HZO between January 1, 1976, and December 31, 1998. Medical records were retrieved for all patients with diagnostic codes related to HZO and its complications. Assigned diagnostic codes were based on Mayo Clinic modifications of the International Classification of Diseases, Ninth Revision, Clinical Modification26 and included codes 530110 (herpes zoster, eye), 530111 (herpes zoster ophthalmicus), 530112 (keratitis, herpetic [zoster]), 530120 (dermatitis, eyelid, herpes zoster), 530130 (keratoconjunctivitis, due to herpes zoster), 530140 (iritis, due to herpes zoster), 530150 (keratouveitis [herpes zoster]), 530151 (infection of cornea by Herpes zoster), 530152 (herpes zoster keratitis), 530153 (herpes zoster keratopathy), 530154 (herpes zoster episcleritis), 530155 (herpes zoster scleritis), 530156 (herpes zoster conjunctivitis), 530157 (herpes zoster keratitis/postherpetic). We also screened charts with the following diagnoses to determine if patients did, in fact, have HZO: 531111 (herpes zoster, face, except eye), 531112 (herpes zoster, cranial nerves), 531113 (herpes zoster, trigeminal), 531121 (herpes, geniculate ganglionitis), 538110 (herpes zoster, nose), 538111 (shingles), 539110 (herpes zoster, late effect of), 539111 (neuralgia, herpetic), 539112 (neuritis, herpetic), and all cases of herpes zoster in which the affected dermatome was not specified. Cases coded as having nonophthalmic trigeminal zoster (ie, Ramsay Hunt syndrome), varicella zoster, and herpes simplex virus were not retrieved. Trained nurse abstractors or one of the coauthors reviewed all medical records to identify all true cases of acute HZO during the study period. The complete medical records for all confirmed cases were then abstracted by a medical student investigator (E.A.S.) to include information on demographics, antiviral and ocular therapy, ocular complications and outcomes of the disease, number of medical visits, and dates of symptom onset, diagnosis, initiation of therapy, and complications. The senior clinician-investigator (K.H.B.) also reviewed all ophthalmologic records for every patient identified as having any complication or adverse outcome other than conjunctivitis. Because specific complications of HZO were treated as statistical end points, we defined each complication and adverse outcome prior to reviewing the records (Table 1). If such an end point occurred and was judged by the senior clinician-investigator to be clearly unrelated to HZO (eg, bilateral open-angle glaucoma 10 years after the onset of HZO), then this end point was excluded from the analysis of HZO-related complications or outcomes.

Most categorical factors were compared between the treated and untreated groups using the χ2 test for independence. The Fisher exact test was used to compare the groups for rare events. Continuous factors were compared between groups using the Wilcoxon rank sum test. Long-term adverse outcome rates were estimated using the Kaplan-Meier method. Comparison of
A manual review of 5295 medical histories with diagnostic codes consistent with potential HZO disclosed 334 confirmed cases. One patient was excluded from further analysis because of ipsilateral anophthalmos before the onset of HZO. Another 10 were excluded because they were involved in a placebo-controlled study of acyclovir. We were unable to establish whether these patients were treated with acyclovir or a placebo. Demographic characteristics for the 323 patients included in the final analysis are shown in Table 2.

A total of 202 patients (63%) had been treated with antivirals and 121 (37%) had not. Mean age and sex distributions were not significantly different between the treated and untreated groups. Short-term complications recorded within 6 months of the onset of symptoms are listed in Table 3. Conjunctivitis was significantly more likely in the treated group of patients, whereas neurotrophic keratitis was more likely to have been diagnosed in the untreated patients. No other significant differences were seen between the untreated and treated groups.

Chronic, inflammatory, and potentially vision-threatening complications of HZO (scleritis, stromal keratitis, corneal edema, uveitis, and glaucoma) were examined together because of their relative infrequency. However, there was no significant difference in the likelihood of developing 1 of these inflammatory complications between the treated and untreated groups (Table 3). As an indirect measure of disease severity in patients affected by 1 of these complications, we analyzed the duration of topical corticosteroid or glaucoma therapy. For those affected patients who received no antiviral medication, the median duration of corticosteroid therapy was 88 days, which was not significantly different than the median duration of 54 days in treated patients (P = .87). Similarly, the difference in the duration of glaucoma therapy in the untreated and treated groups (300 vs 206 days, respectively) was not significant (P = .65).

Among patients who received systemic antiviral therapy, the likelihood of developing 1 of these inflammatory complications was related to the time to initiation of therapy. In those patients who did develop 1 or more of these sequelae, the mean time from symptom onset to treatment was 4.8 days compared with 3.8 days in those patients who did not (P = .006). Patients in the untreated group had fewer follow-up visits with an ophthalmologist within 5 years after the onset of HZO than did patients in the treated group (mean, 5.6 vs 6.9 visits; P = .02).

The cumulative probability of developing a defined adverse outcome was lower in the treated group. Of 121 untreated patients, 6 had HZO-related visual loss, 1 of whom also developed eyelid complications. Another 4 patients had an adverse eyelid outcome without severe visual loss. This was significantly different than the 1 case of severe visual loss and 3 other cases of eyelid sequelae among the 202 patients in the treated group (P = .009). By Kaplan-Meier estimates, the cumulative probability of either adverse outcome at 5 and 10 years was 8.9% in the untreated patients and 2.1% in the treated patients. The cause of visual loss in all cases was corneal scar due to stromal keratitis, neurotrophic keratitis, trichiasis, exposure from eyelid malposition, or a combination of these. However, 1 patient also developed hypotony due to severe uveitis, which may have been contributory. No cases of corneal perforation were recorded.

**RESULTS**

**COMMENT**

Our data indicate that systemic antiviral therapy for acute HZO may decrease the probability of subsequent visual loss and other adverse outcomes. However, previous studies have been in disagreement regarding the effect of acyclovir on the ocular complications of HZO. Cobo et al performed a prospective, randomized study in 71 im-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 323)</th>
<th>Untreated Group (n = 121)</th>
<th>Treated Group (n = 202)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>61.7 ± 19.1</td>
<td>59.3 ± 19.3</td>
<td>63.1 ± 18.8</td>
<td>.09</td>
</tr>
<tr>
<td>Sex, No. (%) of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>136 (42.1)</td>
<td>44 (36.4)</td>
<td>92 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>187 (57.9)</td>
<td>77 (63.6)</td>
<td>110 (54.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated Group (n = 121)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>36 (29.8)</td>
</tr>
<tr>
<td>Epicleritis</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Scleritis</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Epithelial keratitis</td>
<td></td>
</tr>
<tr>
<td>Early dendrites</td>
<td>15 (12.4)</td>
</tr>
<tr>
<td>Mucus plaques</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (14.0)</td>
</tr>
<tr>
<td>Stromal keratitis</td>
<td>15 (12.4)</td>
</tr>
<tr>
<td>Neurotrophic keratitis</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>10 (8.3)</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>27 (22.3)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Muscle palsy</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Retinitis</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Scleritis, stromal keratitis, corneal edema, uveitis, or glaucoma</td>
<td>33 (27.3)</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable.†Fisher exact test.‡Fisher exact test.
munocompetent patients with acute HZO, treated with either 3000 mg per day of acyclovir or placebo. These investigators found that acyclovir reduced the probability of developing dendritic or stromal keratitis, anterior uveitis, and keratic precipitates. Corneal vascularization and scar, neurotrophic keratopathy, iris atrophy, episcleritis, scleritis, and eyelid complications tended to be less frequent in the study group, but these differences were not statistically significant. During 1 year of follow-up, reduction of visual acuity to 20/100 or worse was observed in 4 patients, 3 of whom were in the placebo group.

Herbort et al conducted a clinical trial in which 48 patients with HZO treated with acyclovir were compared with 164 untreated, retrospectively reviewed, historical control patients. Ocular involvement developed in 67% of treated patients, compared with 59% of controls. However, the treated group had only a 4% incidence of serious ocular complications, such as persistent uveitis, stromal or neurotrophic keratitis, corneal perforation, eyelid scarring with consequential effects on the globe, and loss of visual acuity, in contrast to 21% of the controls.

Harding and Porter conducted a trial of 46 patients with HZO randomized to oral acyclovir or placebo, and intraocular involvement was also treated with topical acyclovir. The frequency of intraocular complications was less (30% vs 53%), but not significantly so, in patients receiving acyclovir. At 6 months, the frequency of persistent uveitis was 5% in those receiving acyclovir compared with 42%, a statistically significant difference. Another study of 86 patients treated with systemic and topical acyclovir and followed prospectively found lower ocular complication rates than in previously studied placebo groups or natural history reports.

Despite the prospective, randomized design of the study by Cobo et al, Aylward et al disputed the validity of the former’s conclusions. Included in their criticisms was an apparent dissimilarity in the baseline characteristics between the study and control groups. Aylward et al supported this contention with their own data confirming a lack of any beneficial effect from acyclovir in their experience with 42 patients who were treated with acyclovir adequately (defined as 4000 mg/d commencing within 3 days of the onset of the rash), 35 patients treated inadequately, and 342 untreated patients. The authors admit that a weakness of their own study was the lack of randomization, which may have introduced bias.

Our data revealed a tendency for less frequent inflammatory, short-term complications in patients treated with antiviral therapy. However, similar to the study by Aylward et al, a statistically significant, beneficial effect on these complications was not demonstrable. Because of the retrospective nature of the study, we were not able to grade the severity of individual complications. Therefore, accurately determining whether antivirals blunted the severity of the disease, as was found by Cobo et al, was not possible. We did attempt to indirectly quantify the severity of complications by examining the duration of glaucoma or corticosteroid therapy and again found no significant difference between the 2 groups. Examining the probability of adverse outcomes could be considered another indirect measure of disease severity, and a marked benefit was recognized in the group of patients who received antiviral therapy.

Our study did find a significant difference in the time to initiation of antiviral therapy between those patients who developed serious inflammatory complications compared with those who did not. The patients who developed these complications tended to have a longer delay between symptom onset and the initiation of therapy. This finding supports the concept of “adequate therapy” discussed by Aylward et al, which requires initiation of treatment early in the course of the disease. Other studies of nonophthalmic zoster have also recognized that a beneficial effect is more likely if the drug is started within 3 days of the onset of the rash.

Neurotrophic keratitis was significantly less frequent in treated patients. Why the effect of antivirals on this complication was more evident than the effect on other complications is not readily explainable. Perhaps antivirals have a more potent effect on preventing trigeminal ganglionic damage than on preventing corneal and intraocular inflammation. Certainly this is speculation but not an impossibility, given that the development of neurotrophic disease and inflammatory disease are not necessarily codependent. On the other hand, neurotrophic keratitis is one of the more difficult complications to evaluate, particularly when done retrospectively. In its severe form, the sterile, indolent, interpalpebral ulcers are quite characteristic. Milder forms may not be obvious on examination, so some cases of “other epithelial keratitis” likely represent punctate keratopathy caused by mild neurotrophic disease. Our finding of less frequent severe neurotrophic complications may actually be an indirect indicator of reduced disease severity rather than a decrease in the probability of the complication.

We cannot easily reconcile the finding of more frequent conjunctivitis in treated patients. Because conjunctivitis is often found at the initial visit or very early in the course of the disease, one would expect the antiviral to be neither beneficial nor detrimental. If the study group did indeed have more frequent conjunctivitis, this may represent dissimilarity in baseline disease severity between the 2 groups, a variable that potentially could confound comparisons of complication frequencies.

Most important, with the advantage of long-term follow-up, our study recognized that patients treated with systemic antiviral medication less frequently developed severe visual loss or required eyelid surgery. One may argue that the antiviral therapy was not necessarily the cause of improved outcomes. Patients who were treated with antivirals were seen later in the study period and therefore may have had the privilege of more modern therapy. The more frequent follow-up visits among treated patients (6.9 vs 5.6 visits within 5 years) could also be indicative of more conscientious medical care. However, the difference in adverse outcomes between the 2 groups was highly significant. Furthermore, the therapeutic options to prevent visual loss, for the most part, have been limited to topical corticosteroids and surgical eyelid intervention for the duration of the study period.
The strengths of our study include the large number of subjects, the community-based cohort, which eliminated referral bias, and the potential for long-term follow-up. The latter is a major shortcoming of previous research. A community-based study also better reflects any benefit to the population in a realistic setting. Prior studies may have introduced selection bias by including only those patients who received “adequate therapy.”

Several limitations of this study must be addressed. We employed a retrospective cohort design; thus, we relied entirely on the accuracy and completeness of other physicians’ written records, some of which were up to 25 years old. The treated and untreated groups of patients were also separated by time, so important differences other than the use of antiviral treatment, as previously stated, may present confounding factors. The recognition of statistical end points, namely specific complications and adverse outcomes, relied entirely upon the completeness and duration of follow-up. Although we are confident that our study captured the vast majority of care provided by medical practices to residents in our county, we cannot assume that complications were discovered in patients who did not seek care or who sought care in local ophthalmic practices. Follow-up care by nonophthalmic providers may also reduce our sensitivity in disclosing complications.

Our research has shown that while the frequency of inflammatory ocular complications of HZO, including stromal keratitis and uveitis, may not be less frequent in a treated population, such complications may be associated with a delay in the initiation of antiviral therapy. Severe neurotrophic keratitis, a common cause of irreversible visual loss from this disease, was less likely with antiviral treatment. Even with the potential for decreased effectiveness with delayed treatment, we do urge caution in the decision to administer or withhold therapy to a patient based solely on the duration of symptoms.

A pivotal finding among treated patients was a decrease in the probability of an adverse outcome, most notably severe visual loss. These results may help to justify the cost and routine use of systemic antiviral medications in acute HZO and reinforce the need for prompt diagnosis and therapy. We believe our data also deserve comparison with long-term outcomes from countries where the standard of care may include topical acyclovir, either alone or in combination with oral antiviral medications.

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Corresponding author: Keith H. Baratz, MD, Department of Ophthalmology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: baratz.keith@mayo.edu).

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